A Novel Base Useful for Synthesis of Esters and Macrolides[1]

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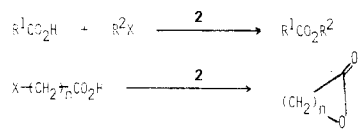
Although a variety of bases have already been examined in the base-promoted preparation of esters and macrolides, they are not always satisfactory in yield and/or simplicity of operation. On the other hand, the anionic species formed from probasic compounds under the conditions of cathodic reduction have been suggested to behave as bases possessing interesting reactivities, though only limited types of probasic compounds such as azobenzenes,[2-5] α,β-unsaturated carbonyl compounds,[6-8] and oxygen[9-12] have been reported so far. We have previously reported that a novel base **2a** ($R = C_2H_5$) is formed by the electroreduction of 2-pyrrolidone (**1**) in DMF (Scheme I), and the base **2a** possesses interesting reactivity to promote the condensation of chloroform with aliphatic aldehydes[13] and selective α-monoalkylation of methyl arylacetates.[14]

In this study, we wish to report that **2** is an efficient base to promote the esterification of carboxylic acids and the formation of macrolides from ω-halo carboxylic acids.



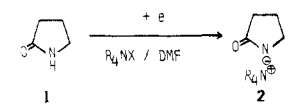
As shown in Scheme II, the addition of a solution of **2a** in DMF into a DMF solution of gibberelic acid (**3**) followed by the treatment of the resulting anion of **3** with ethyl iodide gave the corresponding ester **4** in 77% yield. Although using triethylamine as a base has been reported[15] for the synthesis of some esters, the reaction of **3** under these conditions gave **4** only in 40% yield.

Since this method is highly mild and simple, it is applicable to the synthesis of esters from acids that are not always stable in the usual esterification. Preparation of an ester (**6a,b**) from 6-aminopenicillanic acid derivative **5** is typical of such an example (Scheme III).

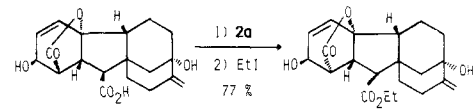
As the other examples (**7-23**) summarized in Table I show, sterically hindered acids (runs 6, 15), a hydroxy acid (run 5), and an amino acid (run 17) were transformed to the corresponding esters in high yields. It is also notable that less reactive *sec*-butyl chloride (run 1) and rather less stable tosylate (run 3) and chlorides (runs 7, 10) could efficiently be used as the alkylating reagents.

Although a number of methods have already been known for the synthesis of esters,[16,17] this new method described above is undoubtedly one of the most reliable ones[18-24] for the preparation of such esters as to be diffi-

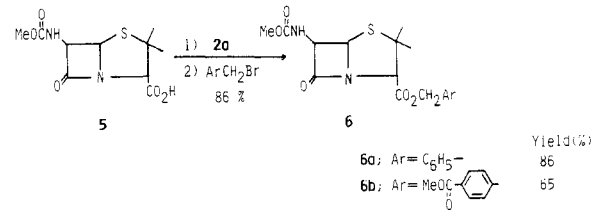
Scheme I



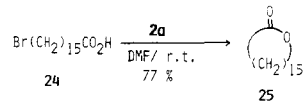
Scheme II



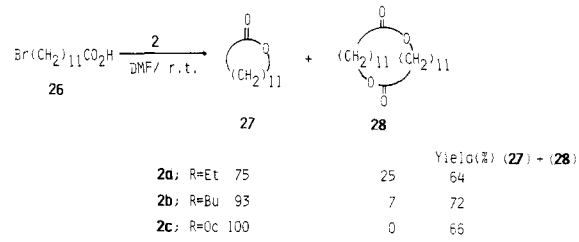
Scheme III



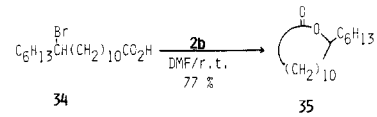
Scheme IV



Scheme V



Scheme VI



Scheme VII

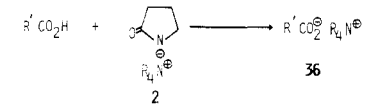


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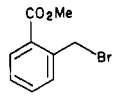
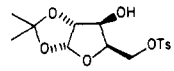
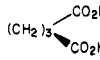
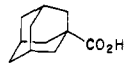
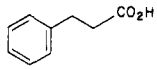
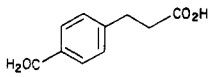
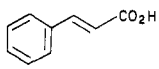
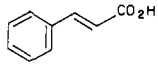
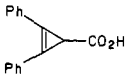
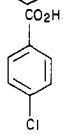
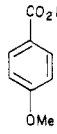
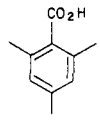
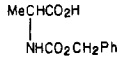
Table I. Synthesis of Esters

run	acid	alkylating	product	yield, %[a,b]	reported yield, %
1	$Me(CH_2)_8CO_2H$	*sec*-BuCl	**7**	83	
2	$Me(CH_2)_8CO_2H$		**8**	80	
3	$Me(CH_2)_2CO_2H$		**9**	94	
4		$PhCOCH_2Br$	**10**	92[c]	
5	$HO(CH_2)_{11}CO_2H$	$PhCH_2Br$	**11**	>99	
6		*i*-PrI	**12**	96	
7		$ClCH_2OMe$	**13**	>99	
8		*i*-PrI	**14**	92[c]	
9		*i*-PrI	**15**	77	
10		$MeSCH_2C$	**16**	95	97[e]
11		$PhCH_2Br$	**17**	99	
12		$PhCH_2Br$	**18**	>99	90[f]
13		$PhCH_2Br$	**19**	>99	
14		$PhCH_2Br$	**20**	>99	
15		*i*-PrI	**21**	>99	100[g]
16			**22**	96	100[h]
17		MeI	**23**	90	93[i]

[a] Isolated Yields. [b] All the products gave satisfactory spectroscopic values for the assigned structures. [c] The products were the corresponding diesters. [d] 1,2-O-(1-Methylethylidene)-5-O-(*p*-tolylsulfonyl)-α-D-xylofuranose. [e] See ref 40. [f] See ref 41. [g] See ref 43. [h] See ref 44. [i] See ref 45.

cultly prepared by the usual methods.

This new method is also useful for the conversion of ω-halo carboxylic acids to the corresponding macrolides.[25] As shown in Scheme IV, the addition of a DMF solution of **2a** (2 mmol) into a solution of 16-bromohexadecanoic acid (**24**) (2 mmol) in DMF (500 mL) at room temperature gave the corresponding hexadecanolide (**25**) in 77% yield.

On the other hand, the reaction of **2a** with 12-bromododecanoic acid (**26**) (Scheme V) under the same reaction conditions gave a mixture of the corresponding dodecanolide (**27**) and the diolide (**28**). Thus, the selective transformation of **26** to **27** has been examined under a

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Table II. Synthesis of Macrolides[a]

$Br(CH_2)_nCO_2H$, n	yield, %[b]	product ratio (macrolide/diolide)
10	70	**29**, **30** (69/31)
11	66	**27** (100/0)
12	75	**31** (100/0)
13	76	**32** (100/0)
14	84	**33** (100/0)

[a] All the products gave satisfactory spectroscopic values for the assigned structures. [b] Isolated yields.

variety of conditions, and it was found that the use of **2b** or **2c** prepared by the electroreduction of **1** using tetrabutylammonium *p*-toluenesulfonate or tetraoctylammonium tetrafluoroborate as the supporting electrolyte leads to the selective formation of dodecanolide (**27**) (Scheme V).

As the other examples are summarized in Table II, the base **2c** is generally efficient for the selective formation of macrolides **29** and **31–33** from ω-bromo carboxylic acids.

Furthermore, the versatility of this new method was also demonstrated by the formation of macrolides having an alkyl group at the position α to the oxygen atom, since the preparation of such macrolides under mild reaction conditions is often difficult due to the low reactivity of the secondary alkyl halides. As shown in Scheme VI, the addition of **2b** into a solution of 12-bromostearic acid (**34**) afforded the corresponding macrolide **35** in a good yield and the formation of the corresponding diolide was not detected.

As depicted in Scheme VII, this new esterification seems to proceed through the intermediary formation of ammonium carboxylates[31] **36** by the reaction of the carboxylic acids with **2**, followed by the intermolecular (formation of esters) or intramolecular (formation of macrolides) reaction of **36** with alkyl halides. This pattern of reaction may also be supported by the effect of bulkiness of ammonium salts observed in the formation of macrolides, since the steric hindrance at the reaction site has been suggested[34] to make the intramolecular reaction more favorable than the intermolecular one.

The method presented in this report is highly useful in the synthesis of esters and macrolides, since the reaction proceeds with high yields under extremely mild conditions.

Experimental Section

Proton nuclear magnetic resonance spectra were measured on a Varian Associates EM-390 or a JEOL JNM-GX-400 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded on Hitachi 260-10 spectrometer. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University.

Materials. Carboxylic acids were commercially available. ω-Halo carboxylic acids[35] and 1,2-*O*-(methylethylidene)-5-*O*-(*p*-tolylsulfonyl)-α-D-xylofuranose[36] were prepared by the known methods.

Preparation of a DMF Solution of 2. A solution of 2-pyrrolidone (**1**) (10 mmol) in 30 mL of DMF containing an ammonium salt (R_4NX, R = Et, Bu, or Oct) (10 mmol) as a supporting electrolyte was placed in a cathodic chamber of an electrolysis cell equipped with platinum electrodes (2 × 2 cm) and a glass filter diaphragm. The anodic solution was 15 mL of DMF containing R_4NX (5 mmol). The preparation of a DMF solution of **2** was accomplished by passing $2F$/mol of electricity through the cell at room temperature under the conditions of constant current (0.2 A).

Synthesis of Esters 4, 6a,b, 7–9, 11–13, and 15–23. A solution of a carboxylic acid (5 mmol) in 5 mL of DMF was added into a solution of **2** (10 mmol) in DMF (20 mL). To this solution was added 10 mmol of an alkyl halide, and the reaction mixture was stirred for 1 h at room temperature. Then, the mixture was poured into an aqueous solution (100 mL) of NaCl and extracted with ether (50 mL × 3). All the products were isolated by distillation (**7**) or by a silica gel column (**4**, **6a,b**, **8**, **9**, **11–13**, and **15–23**) with a mixed solvent of hexane and ethyl acetate (5:1) and identified by spectroscopic comparison with the authentic samples (**7**,[37] **12**,[38] **15**,[39] **16**,[40] **18**,[41] **20**,[42] **21**,[43] **22**,[44] and **23**[45]) and by elemental and spectroscopic analyses (**4**, **6a,b**, **8**, **9**, **11**, **13**, **17**, and **19**).

Synthesis of Diesters 10 and 14. A solution of a dicarboxylic acid (3.3 mmol) in 5 mL of DMF was added into a solution of **2** (10 mmol) in 20 mL of DMF. Into this solution was added 10 mmol of an alkyl halide, and the mixture was stirred for 1 h at room temperature. After the usual workup, the products **10** and **14** were isolated by silica gel column (5:1 hexane–EtOAc) and identified by elemental and spectroscopic analyses.

4: IR (KBr) 3350, 1735 cm^{-1}; NMR (Me_2SO-d_6) δ 6.39 (d, J = 9 Hz, 1 H), 5.81 (d d, J = 3.9, 9 Hz, 1 H), 5.56 (d, J = 6 Hz, 1 H), 5.20 (br s, 1 H), 4.20 (q, J = 7.5 Hz, 2 H), 3.80–4.02 (m, 1 H), 3.33 (s, 2 H), 3.10 (d, J = 9 Hz, 1 H), 2.60 (d, J = 9 Hz, 1 H), 1.40–2.10 (m, 7 H), 1.06 (t, J = 7.5 Hz, 3 H), 1.10 (s, 3 H). Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.33; H, 6.92.

6a: IR (neat) 3350, 1790, 1735 cm^{-1}; NMR ($CDCl_3$) δ 7.38 (s, 5 H), 5.66 (m, 1 H), 5.46 (m, 1 H), 5.15 (s, 2 H), 4.43 (s, 1 H), 3.67 (s, 3 H), 1.58 (s, 3 H), 1.39 (s, 3 H). Anal. Calcd for $C_{17}H_{20}NO_5S$: C, 58.27; H, 5.75; N, 4.00. Found: C, 58.20; H, 5.62; N, 3.89.

6b: IR (neat) 1790, 1730 cm^{-1}; NMR ($CDCl_3$) δ 8.10 (m, 1 H), 7.71–7.30 (m, 3 H), 5.70 (s, 2 H), 5.61–5.83 (m, 1 H), 5.00–5.31 (m, 1 H), 4.30–4.48 (m, 1 H), 4.00 (s, 3 H), 3.73 (s, 3 H), 1.60 (s, 3 H), 1.21 (s, 3 H). Anal. Calcd for $C_{19}H_{22}NO_7S$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.62; H, 5.56; N, 3.45.

7: bp 135–136 °C (10 mmHg); IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.83 (m, 1 H), 2.27 (t, J = 7 Hz, 2 H), 1.10–1.73 (m, 19 H), 0.83–1.00 (m, 6 H).

8: IR (neat) 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 8.07–7.96 (m, 1 H), 7.60–7.33 (m, 3 H), 5.53 (s, 2 H), 3.90 (s, 3 H), 2.39 (t, J = 7 Hz, 2 H), 1.67 (m, 2 H), 1.27 (m, 12 H), 0.70 (m, 3 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.27; H, 8.98.

9: IR (neat) 3460, 1740 cm^{-1}; NMR ($CDCl_3$) δ 5.90 (d, J = 2 Hz, 1 H), 4.59 (d, J = 2 Hz, 1 H), 4.50–4.11 (m, 4 H), 3.30 (m, 1 H), 2.40 (t, J = 5 Hz, 2 H), 1.87–1.17 (m, 2 H), 1.50 (s, 3 H), 1.33 (s, 3 H), 0.93 (t, J = 6 Hz, 3 H). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.09; H, 7.74.

10: IR (neat) 1740, 1710 cm^{-1}; NMR ($CDCl_3$) δ 8.03–7.43 (m, 10 H), 5.36 (s, 4 H), 2.67 (t, J = 7 Hz, 4 H), 2.13 (m, 2 H). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.40; H, 5.44.

11: IR (KBr) 3320, 1735 cm^{-1}; NMR (CCl_4) δ 7.33 (s, 5 H), 5.05 (s, 2 H), 3.53 (t, J = 7.5 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 1.73–1.13 (m, 18 H). Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.48; H, 9.95.

12: IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 5.00 (m, 1 H), 2.00–1.66 (m, 15 H), 1.23 (d, J = 7 Hz, 6 H).

13: IR (neat) 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.20 (s, 5 H), 5.20

(31) The high reactivity of ammonium carboxylates[32] **36** has been reported, though the synthesis of **36** is often troublesome.[33]

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(s, 2 H), 3.37 (s, 3 H), 3.07-2.53 (m, 4 H). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.39.

14: IR (neat) 1730, 1720 cm^{-1}; NMR ($CDCl_3$) δ 8.00 (d, J = 9 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H), 5.43-4.83 (m, 2 H), 3.00 (t, J = 7 Hz, 2 H), 2.60 (t, J = 7 Hz, 2 H), 1.37 (d, J = 7 Hz, 6 H), 1.20 (d, J = 7 Hz, 6 H). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.92; H, 8.00.

15: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.73 (d, J = 16.5 Hz, 1 H), 7.27-7.60 (m, 5 H), 6.42 (d, J = 16.5 Hz, 1 H), 5.13 (s, 2 H), 2.27 (s, 3 H).

16: IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 7.40-7.07 (m, 4 H), 7.60 (d, J = 16 Hz, 1 H), 6.30 (d, J = 16 Hz, 1 H), 5.13 (s, 2 H), 2.27 (s, 3 H).

17: mp 67-68 °C; IR (KBr) 1720 cm^{-1}; NMR ($CDCl_3$) δ 7.77-7.17 (m, 10 H), 7.27 (s, 5 H), 5.13 (s, 2 H), 2.70 (s, 1 H). Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.93; H, 5.60.

18: IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 7.97-7.80 (m, 1 H), 7.57-7.20 (m, 8 H), 5.38 (s, 2 H). Anal. Calcd for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.49. Found: C, 68.01; H, 4.21.

19: IR (neat) 1720 cm^{-1}; NMR (CCl_4) δ 8.00 (d, J = 9 Hz, 2 H), 7.37 (d, J = 9 Hz, 2 H), 7.33 (s, 5 H), 5.27 (s, 2 H).

20: IR (neat) 1720 cm^{-1}; NMR (CCl_4) δ 8.00 (d, J = 9 Hz, 2 H), 7.47-7.03 (m, 5 H), 6.83 (d, J = 9 Hz, 2 H), 5.27 (s, 2 H), 3.80 (s, 3 H).

21: IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.87 (s, 2 H), 5.27 (m, 1 H), 2.33 (s, 9 H), 1.35 (d, J = 7 Hz, 6 H).

22: IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 8.13-7.90 (m, 2 H), 7.53-7.17 (m, 3 H), 6.33-5.67 (m, 1 H), 5.50-5.07 (m, 2 H), 4.87-4.67 (m, 2 H).

23: IR (neat) 3350, 1740, 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.53 (s, 5 H), 5.18 (s, 2 H), 3.76 (s, 3 H), 1.39 (d, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ -34.8° (c 2.5, CH_3OH) [lit.[45] $[\alpha]^{23}_D$ -35°].

Synthesis of Macrolides 25, 27, 29, 31, 32, and 33. The preparation of **2a-c** in DMF was carried out under the same reaction conditions as described above. Into a DMF solution (500 mL) of an ω-bromo carboxylic acid (1 mmol), a solution of **2** (2 mmol) in 6 mL of DMF was added at -60 °C, and the reaction mixture was stirred for 24 h at room temperature. After the solvent was evaporated, the products were isolated through silica gel column with a mixed solvent of hexane and ethyl acetate (5:1). The ratios of macrolides **27** and **29** and diolides **28** and **30** were determined by the relative intensity of protons at the position α to oxygen by using 400-MHz ^1H NMR spectrometer.

25:[27] IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.12517 (t, J = 5.6 Hz, 2 H), 2.32304 (t, J = 6.8 Hz, 2 H), 1.66930-1.26106 (m, 26 H); mass speectrum, m/e 254 (M^+).

27:[46] IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.15632 (dd, J = 6.5, 5.3 Hz, 2 H), 2.37373-2.34289 (m, 2 H), 1.69190-1.34595 (m, 18 H); mass spectrum, m/e 198 (M^+).

28:[46] mp 80.5-82 °C; IR (neat) 1732 cm^{-1}; NMR ($CDCl_3$) δ 4.10440 (t, J = 5.9 Hz, 4 H), 2.31235 (t, J = 7 Hz, 4 H), 1.64976-1.27633 (m, 36 H); mass spectrum, m/e 396 (M^+).

29:[46] IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.19891 (dd, J = 6.3, 5.3 Hz, 2 H), 2.38502-2.35327 (m, 2 H), 1.72762-1.36274 (m, 16 H); mass spectrum, m/e 184 (M^+).

30:[46] mp 72-73 °C; IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.10349 (t, J = 5.9 Hz, 4 H), 2.31816 (t, J = 6.8 Hz, 4 H), 1.65831-1.24213 (m, 32 H); mass spectrum, m/e 368 (M^+).

31:[29b] IR (neat) 1733 cm^{-1}; NMR ($CDCl_3$) δ 4.14746 (t, J = 5.4 Hz, 2 H), 2.39144-2.36029 (m, 2 H), 1.68701-1.26747 (m, 20 H); mass spectrum, m/e 212 (M^+).

32:[47] IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.13769 (t, J = 5.4 Hz, 2 H), 2.36701-2.33556 (m, 2 H), 1.69343-1.32892 (m, 22 H); mass spectrum, m/e 226 (M^+).

33:[29b] IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.13402 (t, J = 5.6 Hz, 2 H), 2.33006 (t, J = 6.0 Hz, 2 H), 1.67755-1.26381 (m, 24 H); mass spectrum, m/e 240 (M^+).

35:[48] IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.97951-4.91051 (m, 1 H), 2.49464-2.17587 (m, 2 H), 1.77373-0.85723 (m, 33 H); mass spectrum, m/e 282 (M^+).

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Facile Preparation of Nitrones by Electrochemical Oxidation of *N*-Hydroxy Secondary Amines Using Halogen Ions as Mediators[1]

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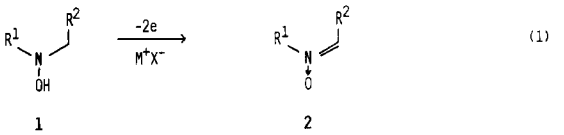
Nitrones **2** are versatile 1,3-dipoles useful for the construction of nitrogen heterocycles.[2] Synthesis of nitrones by oxidation[3] of *N*-hydroxy secondary amines **1** is not always convenient owing to the requisite of using an excess amount of the oxidizing agents and the resulting troublesome workup. In our continuing study on the anodic oxidation using mediators,[4] we have found a new electrooxidative method of synthesis of **2** from **1** (eq 1).



(1)

1 **2**

The procedure is simple and practical as exemplified by the oxidation of *N*-hydroxypiperidine (**1a**). Thus, nitrone **2a** was prepared by passing a constant current through a solution of **1a** in methanol containing sodium iodide as a supporting electrolyte (M^+X^-). The results obtained under several conditions are shown in Table I indicating that using even a catalytic amount of iodide as the supporting electrolyte gave satisfactory results (runs 1, 2, 4, and 5), whereas bromide and chloride (runs 6 and 7) gave poor results.

On the basis of these facts, the formation of **2a** can reasonably be explained by the working hypothesis in which I^- is anodically oxidized to the active species "I^+",[5,6] and the intermediate **3** formed from the reaction of **1a** with "I^+" yielded **2a** through elimination of HI catalyzed by a cathodically generated base[7] (Scheme I).

Since I^- regenerated is again reoxidized to "I^+", only a catalytic amount of NaI is enough to complete the oxidation of **1a** to **2a**. The formation of **2a** may be, however,

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